UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,507	07/15/98	EIJSINK	V 1380-122PCT

HM12/0929

BIRCH STEWART KOLASCH & BIRCH
P O BOX 747
FALLS CHURCH VA 22040-0747

EXAMINER	
SLOBODYANSKY, E	
ART UNIT	**PAPER NUMBER**
1652	12

DATE MAILED: 09/29/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/068,507	Eijsink et al.
Examiner	**Group Art Unit**
Elizabeth Slobodyansky	1652

☒ Responsive to communication(s) filed on *Feb 17, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application is a 371 of PCT/NO96/00266.

The preliminary amendment filed concurrently with the application inserting reference to the prior applications and amending claims 4-6, 8-10 and 12-14 has been entered.

The amendment filed February 1, 1999 has been placed in the file and the following parts thereof have been entered: replacement of the Sequence Listing and the amendments to the specification. The amendments to the claims did not mach the claims.

The amendment filed February 17, 1999 replacing the Sequence Listing has been entered.

Claims 1-15 are pending.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or

other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

This application has been filed with formal drawings which have been approved by Draftsman.

Claim Objections

Claim 12 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). However, the claim was treated as if it were properly written in the interests of compact prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, with dependent claims 2-10 and 12-14, and claim 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the expression system based on sakacin P gene cluster *Lactobacillus* system, does not reasonably provide enablement for functional equivalents/analogues to promoters, genes and peptides involved in the production of sakacin P. It does not reasonably provide enablement for a system based on other bacteriocins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claim 1 recites functional equivalents/analogues to promoters and peptides and claim 15 recites functional analogues of genes, respectively. Although the specification teaches sakacin P gene cluster that can be induced by sakacin P, it lacks guidance as to where, and what type of (i.e, what amino acid substitute into, remove from or add to the known sequence) changes in amino acid residues will result in retention of the requisite activity. ~~While there is a great number of possible mutants, it is *a priori* unpredictable as to which mutant will exhibit an amidase activity. Particularly,~~ Applicants do not teach the properties that would distinguish such functional equivalents/analogues from nisin and its functional equivalents/analogues as well as other lantibiotics such as subtilin, epidermin, etc. In other words the specification does not teach what makes nisin but not, for example, subtilin, the bacteriocin that is outside of the scope of the claim. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The gene clusters involved in the production of bacteriocins are organized differently and the specification does not

teach what are the specific genes that are at minimum necessary for the heterologous expression. In addition, while the specification enables for an inducer that is sakacin P, it does not enable for other inducers that are unmodified peptides (enzymes) and are products of other genes of the sakacin gene cluster, for example. Therefore, the breadth of these claims is much larger than the scope enabled by the specification. Therefore, one of ordinary skill would require guidance, such as information regarding the specific amino acid changes which would result in the preservation of a sakacin promoter activity and what are other inducers and regulatory genes that can be used in the expression system of the present invention, in order to make and use a variant sequence of sakacin or other inducers and regulatory genes in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, with dependent claims 2-10 and 12-14, and claim 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, with dependent claims 2-10 and 12-14, and claim 15 recite functional equivalents/analogues. There are no clear assigned definitions of terms

"equivalents/analogues" in the art. Furthermore, it is unclear which particular "function is implied.

Claim 1 recites "unmodified peptide". A peptide can be modified in different ways. Amendment to "a mature bacteriocin that is the product of the gene cluster and is not posttranslationally modified", for example, would clarify the claim.

Claim 1 recites "the peptide having the sequences shown in Seq. id. No.1 and Seq. id. No. 2". SEQ ID NO:1 is an amino acid sequence and SEQ ID NO:2 is a nucleotide sequence. A peptide "has" an amino acid sequence and "is encoded" by a nucleotide sequence.

Regarding claim 15, the term "similar" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "similar"), thereby rendering the scope of the claim unascertainable. Furthermore, claim 15 is indefinite in that the provided drawing (Figure 1) does not adequately define the claimed genes in view of indefinite end positions and not defined sequences.

Claims 12-14 provide for the use of the gene expression system/host cells, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 12-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Diep et al. (1994) or Tichaczek et al.

Claim 11 is drawn to peptide that has the amino acid sequence of SEQ ID NO:1.

Diep et al. (1994, form PTO-1449) disclose the gene encoding plantaricin A and the amino acid sequence of the preproplantaricin A (page 162, Figure 1).

Tichaczek et al.(form PTO-1449) disclose the gene encoding sakacin P and the amino acid sequence thereof. SEQ ID NO:1 is identical to a fragment of said amino acid sequences. As "has" is an open language, the amino acid sequences encoded by plantaricin A gene and sakacin P gene read on claim 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1, with dependent claims 2-10 and 12-14, and claim 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diep et al. (1995).

Diep et al. (1995, form PTO-1449) teach that plantaricin A induces its own production by stimulating transcription of the *plnABCD* operon (abstract; page 632, left-hand column, 1st paragraph; page 634, right-hand column; page 636, right-hand column, 1st paragraph). They teach that two-component regulatory systems located in nisin, subtilin, epidermin and sakacin A gene clusters are essential for the production of these bacteriocins (page 632, left-hand column, 2nd paragraph). They teach that production of bacteriocins is a regulated process. They teach that bacteriocin production in *Lactobacillus plantarum* C11 is an inducible process. They teach the heterologous expression of *plnABCD* that can be induced by plantaracin A (page 637, paragraph bridging two columns; page 638, left-hand column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to proceed with the heterologous expression of *plnABCD* wherein the gene encoding plantaracin A is modified or replaced with a gene encoding a

desired protein. Motivation to use plantaracin A promoter and *plnBCD* genes is provided by Diep et al. who teach the autoinduced heterologous expression of plantaracin A.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kuipers et al. (US 5,914,248) teach a method for the controlled expression of a gene based on the nisin promoter and regulatory genes of the nisin gene cluster.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD

September 16, 1999